Geological Society of America
Special Paper 155

Cadmium-Zinc Interactions: Implications for Health

HAROLD H. SANDSTEAD

AND

LESLIE M. KLEVAY
USDA Human Nutrition Laboratory
P.O. Box D, University Station
Grand Forks, North Dakota 58201

INTRODUCTION

Cadmium and zinc are chemically similar (Cotzias and others, 1961; Cotton and Wilkinson, 1966). They therefore compete with one another for a variety of ligands (Pulido and others, 1966a; Gunn and others, 1968). Because cadmium is considered to have only adverse effects in biological systems (Friberg and others, 1971) and zinc is an essential nutrient (Sandstead, 1973), the significance of their competitive interactions for health merits investigation.

In this paper we will examine the hypothesis that competition between zinc and cadmium for biological ligands has important implications for health.

ZINC AND CADMIUM IN THE ENVIRONMENT

Cadmium is a relatively rare element. Its average concentration in the Earth's crust is about 0.5 ppm (Heindl, 1970). In nature it is closely associated with zinc (Friberg and others, 1971). The zinc:cadmium ratio of most minerals and soils ranges from 100:1 to 12,000:1 (Bowen, 1966; Schroeder and others, 1967).

In the United States, cadmium is obtained commercially only as a by-product during the processing of zinc-bearing ores (Heindl, 1970). Its production has risen steadily during the past three decades (Moulds, 1969). This growth can be described by the equation $y = 0.21x - 1.81$, where y represents the annual production in millions of pounds and x is the year minus 1900.

Sixty percent (8 million pounds in 1968) of the cadmium produced each year is used for electroplating (Heindl, 1970), and products plated with cadmium are widely used throughout the United States (Flick and others, 1971). Such cadmium-

plated products and cadmium-containing materials may be hazardous to man in certain situations. Examples of such situations include the cutting of cadmium-plated bolts with a torch (Zavon and Meadows, 1970) or the use of cadmium-containing silver solder in a poorly ventilated space (Winston, 1971). Inappropriate use of cadmium-plated refrigerator shelves for grilling food has also resulted in poisoning by ingestion (Baker and Hafner, 1961).

Thirteen percent (Heindl, 1970) of the annual production of cadmium is used in pigments incorporated into plastics, paints, enamels, lacquers, and printing ink. The manufacture of batteries accounts for 3 percent. Cadmium also enters the environment through its presence in the fumes of lead and copper smelters.

Cadmium salts of stearic acid are used (2.5 million pounds in 1968) as stabilizers (Heindl, 1970) in thermoplastics, such as polyvinylchloride, a material widely used in the packaging of food. Whether the cadmium in such plastics can migrate into foods is apparently unknown. It is known, however, that phthalate esters have leached into human blood from the polyvinylchloride bags in which it was stored (Jaeger and Rubin, 1972). The use of cadmium in plastics may have decreased since the introduction of dioctyl tin stabilizers (Wood, 1968).

Plastic (polyvinylchloride) pipes are being used increasingly. To our knowledge, reliable data regarding the extraction of cadmium from such pipes by water have not been published. On the other hand, it is well known that cadmium in solder and galvanizing dissolves in soft water passing through water pipes. The consequences of such a phenomenon have been illustrated by the finding of 8.3 ppm cadmium in running water from the cold water tap and 15 to 77 ppm in cold water that had been stagnant in the pipes of a municipal hospital. Hot water contained 21 ppm (Schroeder and others, 1967).

The close association of cadmium and zinc is also important in agriculture. Because it is difficult to remove cadmium from zinc, the zinc sulfate used to manufacture super phosphate fertilizers contains 15 to 21 ppm cadmium (Hammer and others, 1971). The fertilizer itself may contain 2 to 20 ppm cadmium. Use of superphosphate fertilizers releases 50,000 to 500,000 lb of cadmium into the environment each year (USDA and TVA, 1964). Another potential source of cadmium in food is sewer sludge, a material rich in nitrogen phosphate, macro-elements, trace metals, and toxic heavy metals (Larson and others, 1972). Cadmium concentrations of sludge from various sources have been found to range from 6 to 369 ppm. Sources of the sludge appear to be responsible for these wide differences. When the amount of industrial wastes is high, the cadmium content is increased. The entry of this cadmium into plants is a subject of current investigation.

ENTRY OF CADMIUM INTO MAN

Cadmium enters man from several sources (Table 1). These include air, cigarette smoke, drinking water, and food. The contributions of these various sources to the body burden of cadmium are dependent on the amount of cadmium in the source material, the physiochemical characteristics of the source material that affect solubility of the cadmium, and factors in the body, which affect solubility of cadmium and its movement across the intestinal mucosa and through the

TABLE 1. ENVIRONMENTAL LEVELS: USUAL INTAKE AND RETENTION OF CADMIUM

Range	Usual intake/day (μg)
Air 0.01 to 0.2 μg/m^3	0.5
Cigarette smoke 0.7 to 0.8 μg/whole cigarette	3.0
Drinking water 0 to 30 μg/l	5.0
Food 30 to 200 μg/day	50
Usual total intake/day	58.5
Nonurban, nonsmoking, low-cadmium foods	32
Urban, smoking (3 pk), high-cadmium foods	190

Retention			
Inhalation	10 to 40%; 3.5 μg × 0.25 =	0.875	μg
Ingestion	3 to 8%; 55.0 μg × 0.05 =	2.750	μg
Total		3.625	μg
Excretion (of that absorbed)	Stool 10%; 3.625 =	0.360	μg
	Urine =	1.500	μg
Total		1.860	μg
Net daily retention		1.765	μg
Net 50-yr retention		32.3	mg
Net 50-yr renal cortical Cd		50	μg/g of tissue

body. Thus the factors that influence the total body burden of cadmium are complex. Because food and water are the major sources of cadmium, those factors that influence the availability of cadmium for intestinal absorption are the most important.

The usual daily intake of cadmium by urban man has been estimated (Friberg and others, 1971). The amounts of cadmium in air, cigarette smoke, drinking water, and food are shown in Table 1. From these data one can estimate the probable daily absorption, excretion, and retention of cadmium. Thus an urban adult could retain 1.77 μg of cadmium daily, an amount sufficient to result in a retention of 32 mg of cadmium in 50 yr. The renal cortex of such an individual would contain approximately 50 ppm, an amount in the range found by Tipton on analysis of renal tissue from urban men (Schroeder and others, 1967). It has been suggested by Friberg that a renal cortical concentration of approximately 200 ppm is necessary before gross pathological effects (proteinurea) occur. This level of renal cadmium correlates with a body burden of 120 mg. To accumulate 120 mg of cadmium in 50 yr, a dietary intake of approximately 160 μg daily would be necessary if the intake from the other sources listed in Table 1 were similar. This level of intake probably does occur in some heavy-smoking urban individuals who consume foods rich in cadmium (Schroeder and Balassa, 1961).

RELATIONSHIP OF DIETARY ZINC AND DIETARY CADMIUM

Man obtains most of his zinc from his diet. As noted above, this is also true for cadmium. The amount of zinc in the diet may vary widely depending on the diet composition. Some diets reported in the literature (Sandstead, 1973) contained 5 to 20 mg.

The availability of dietary zinc for absorption is also influenced by the diet composition. The digestability of the food is a crucial factor. Hence zinc in meat, sea food, or milk products (which are readily digested by normal man) is considerably more available than zinc in grains, legumes, and other vegetables, which contain phytate or other ligands that can complex with zinc to form insoluble chelates in the alkaline environment of the small intestine. Presumably, cadmium behaves in a manner similar to zinc in the intestinal milieu. Its low availability for intestinal absorption from food (3 to 8 percent) compared with an approximately 20 to 30 percent availability of zinc (Sandstead, 1973) suggests that, in fact, most of the cadmium present in food is firmly bound to insoluble ligands during the process of digestion, with the result that 95 percent or more of dietary cadmium is excreted in the stool.

Reported zinc (Schroeder and others, 1967) and cadmium (Schroeder and Balassa, 1961) contents of selected foods are listed in Table 2. Though the absolute amounts of these two elements in food are important, their availability from foods is perhaps an even more important factor as far as the toxic effects of food cadmium and the protective effects of zinc are concerned.

Observations on the zinc:cadmium ratio in wheat, whole-wheat flour, and white flour indicate that the distributions of zinc and cadmium within the wheat grain are different. As wheat is refined, the ratio decreases from 120:1 in wheat to 65:1 in whole-wheat flour to 26:1 in white flour (Schroeder and others, 1967). Presumably, a similar relationship is present in other grains. The implication of the difference in distribution of zinc and cadmium in raw grain is that refining decreases the relative amount of the essential nutrient, zinc, while increasing the relative amount of the toxic element, cadmium, in the final food product.

TABLE 2. CONCENTRATIONS OF Zn* AND Cd† IN FOODS (PPM)

	Oyster	Canned tuna	Beef steak	Beef liver	Pork chops
Zn	1487.0	17.4	56.6	39.2	3.6
Cd	0.65	0.06	0.024	0.20	0.025
	Homog. milk	**Whole egg**	**White flour**	**Corn meal**	**Lima beans**
Zn	0.1–0.5	20.8	8.9	9.0	31.5
Cd	tr	tr	0.059	0.065	0
	Potatoes	**Kidney beans**	**Lettuce**		
Zn	8.7	0.80	1.6		
Cd	0	0.052	0.17		

*Data from Schroeder and others (1967).
†Data from Schroeder and Balassa (1961).

ZINC AND CADMIUM INTERACTIONS IN THE BODY

Within the body, zinc and cadmium are primarily complexed with intracellular ligands. Zinc is necessary for the activity of many metalloenzymes and metal-dependent enzymes (Parisi and Vallee, 1969). In addition, zinc is complexed with nucleoproteins and other nonenzyme proteins and influences their tertiary and (or) quaternary structure. In liver, kidney, and intestinal mucosa, zinc is also bound to metallothionine. Metabolically, zinc is essential for the synthesis of nucleic acids (Sandstead and others, 1972; Terhune and Sandstead, 1972) and proteins (Hsu and others, 1969), functions that may explain its role in growth (Sandstead and others, 1967) and tissue repair (Sandstead and others, 1970).

Cadmium, in contrast to zinc, has no known metabolic function. Within cells its only known effects are those of toxicity. Cadmium binds firmly to mercapto groups of proteins and is thus firmly bound to metallothionine, a protein with many free sulfhydryl groups (Pulido and others, 1966b; Kagi and Vallee, 1961). The affinity of cadmium for mercapto groups is many times that of zinc. Thus it may displace zinc from sulfur ligands and may inhibit certain reactions dependent on the presence of zinc.

Equine kidney metallothionine has been found to contain 59,500 ppm cadmium, 16,900 ppm zinc, 310 ppm iron, and 1,500 ppm copper, a total of 8.4 G-atoms of metal per 10,000 mol. wt. The free sulfhydryl groups, due to a large proportion of cysteinyl residues, are 26 per mole. As the function of metallothionine has not been fully clarified and as it appears to protect sensitive enzyme systems within cells by binding with cadmium and other metals, metallothionine may be considered a "scavenger protein" until some other function is identified.

The fact that cadmium binds firmly to sulfhydryl groups has suggested to us that it may react with the enzyme superoxide dismutase. This enzyme has two free sulfhydryl groups (Hartz and Deutsch, 1972) in addition to two atoms of zinc and two of copper (Carrico and Deutsch, 1970) per molecule.

Superoxide dismutase catalyses the reaction $O_2^- + O_2^- + 2H^+ \rightarrow O_2 + H_2O_2$ (McCord and Fridovich, 1969), thus protecting the electron transport system of cells from the accumulation of free radicals (McCord and Fridovich, 1970). It has been postulated that free radicals may damage cells and thus accelerate the aging process (Harman, 1956). In addition, they are thought to contribute to the cellular damage caused by ionizing radiation (Little, 1968).

It seems possible that cadmium may decrease the activity of superoxide dismutase, either by binding its sulfhydryl groups and thus altering the tertiary structure of the molecule, or perhaps by displacing zinc or copper from their sites on the protein. The possible consequences for health of such a reaction by cadmium are obvious, if the free radical theory of aging is true. Metallothionine, through its "scavenger" effect, may tend to protect superoxide dismutase and other susceptible enzymes from the injurious effects of cadmium and excesses of other transition metals. The postulated binding of sulfhydryl groups of superoxide dismutase by cadmium has been shown for several other enzymes (Simon and others, 1947). The adverse effects of cadmium on oxidative phosphorylation (Jacobs and others, 1956) may be explained either by disruption of the transport of electrons (McCord and Fridovich, 1970), if free radicals accumulate secondary to inhibition of superoxide dismutase, or by the binding of the dithiol groups

of lipoamide dehydrogenase. This latter enzyme is readily inhibited by lead (Ulmer and Vallee, 1969) and is therefore presumably susceptible to inhibition by cadmium. It is part of the macro-molecular complex of enzymes that synthesize acetyl coenzyme A and succinyl coenzyme A from pyruvate and α-keto glutarate, respectively.

To our knowledge, an in vivo inhibition by cadmium of enzymes activated by zinc has not been shown. Even so, it is probable that cadmium does inhibit certain of the metabolic functions of zinc. The protective effect of zinc—against the toxic effects of cadmium on testes (Gunn and others, 1968), against cadmium induced sarcomas (Gunn and others, 1964), and the reversibility of cadmium-induced hypertension in rats by parenterally administered zinc chelate (Na_2Zn–CDTA) (Schroeder and others, 1968)—supports this thesis.

Under usual circumstances, roughly one-third of the body cadmium is found in the renal cortex. There it is concentrated in the proximal tubular cells of the nephron. High concentrations of cadmium in these cells have adverse effects on their reabsorptive function. In man an extreme manifestation of the toxic effects of cadmium on the renal tubule is iti-iti disease. Patients with this disease come from a region in Japan where the water is contaminated with zinc and cadmium. Thus rice raised in the water contains high levels of these elements. The clinical features of iti-iti include an "adult Fanconi's" syndrome similar to that which has been observed associated with injury to the renal tubules by other toxic metals. Tubular reabsorption of glucose, amino acids, protein, phosphate, and certain electrolytes may be impaired. Osteomalacia, microfractures, bone pain, and crippling deformities occur (Friberg and others, 1971).

Another organ that is adversely affected by cadmium in experimental animals is the arterial wall. Chronic feeding (1 yr) of low concentration (5 ppm) of cadmium will produce hypertension in Long-Evans female rats (Schroeder and others, 1968). It seems probable that the hypertension observed is a consequence of a direct effect of cadmium on the vessel wall, as acutely injected cadmium has been shown to have an immediate vasoconstrictor effect on testicular vessels (Gunn and others, 1968), on the isolated hind limb of the rat (Perry and others, 1967), and on the intra-arterially perfused intact rat (Perry and others, 1970). In addition, cadmium is bound by the tissues of the perfused hind limb and to isolated strips of aorta (Perry and others, 1970). A direct effect of cadmium on the arteries of the renal cortex is inferred by the finding that the plasma renin activity (Perry, 1971) and sodium retention of rats injected with cadmium are increased (Perry and others, 1971). These findings may provide an explanation for the hypertension observed in Long-Evans rats that were fed cadmium chronically.

In man, a causal role for cadmium in the genesis of hypertension is less clear. Perry (1971) has reviewed the evidence for this. He noted that renal concentrations of cadmium vary with the geographic origin of the individual (Perry and others, 1961), and that hypertensive Americans were found by Schroeder (1965) to have higher concentrations of renal cadmium than nonhypertensive Americans; in a later study, Morgan (1969) did not find such a relationship. On a world-wide basis, the incidence of hypertension is greater in those populations in which higher concentrations of renal cadmium occur. More recent epidemiologic studies of individuals exposed industrially to cadmium have not shown a relationship between

cadmium and hypertension (Hammer and others, 1971). A similar negative relationship has been found between the intake of cadmium in milk and cardiovascular disease (Pinkerton and others, 1971).

A recent autopsy study (Voors and others, 1975) of individuals from the Piedmont region and coastal plain of North Carolina has revealed a positive correlation between renal cortical cadmium:zinc ratio and the severity of atherosclerosis as judged by examination of the arteries at autopsy. Additionally, it has shown a marginal positive correlation between hypertension as indexed by cardiac weight and the renal cortical cadmium:zinc ratio. This latter relationship appears related either to residence (coastal plain) or race (black). The fact that the coastal plain is a "soft water area" is also of interest in this regard. In Voors and others' (1975) study, a statistical relationship between renal tissue cadmium and atherosclerosis or hypertension was not found. Thus Voors demonstrated the importance of considering the interaction between zinc and cadmium in relation to disease. It seems possible that the failure of epidemiologic studies to find a relationship between cadmium exposure and hypertension or atherosclerosis may have been due to a failure to consider the cadmium:zinc ratio instead of cadmium alone. The experimental findings from animal studies noted above certainly support the hypothesis that cadmium may have adverse cumulative effects on the cardiovascular system.

Additional investigation of the relationships between zinc and cadmium in man is needed. Such research should be done with the recognition that sodium, potassium, lithium, copper, calcium, and magnesium may possibly influence the physiologic effects of the zinc:cadmium interaction. Failure to control these additional variables may result in data that is confusing and may tend to obscure the central issue: the role of cadmium in human disease.

REFERENCES CITED

Baker, T. D., and Hafner, W. G., 1961, Cadmium poisoning from a refrigerator shelf used as an improvised barbecue grill: Pub. Health Rept., v. 76, p. 543–544.

Bowen, H.J.M., 1966, Trace elements in biochemistry: London, Academic Press, 241 p.

Carrico, R. J., and Deutsch, H. F., 1970, The presence of zinc in human cytocuprein and some properties of the apoprotein: Jour. Biol. Chem., v. 245, p. 723–727.

Cotton, F. A., and Wilkinson, G., 1966, Advanced inorganic chemistry: New York, Interscience, p. 600–611.

Cotzias, G. C., Borg, D. C., and Selleck, B., 1961, Virtual absence of turnover in cadmium metabolism: ^{109}Cd studies in the mouse: Am. Jour. Physiol., v. 201, p. 927.

Flick, D. F., Krabill, H. F., and Dimitroff, J. M., 1971, Toxic effects of cadmium: A review: Environmental Research, v. 4, p. 71–85.

Friberg, L., Piscator, M., and Nordberg, G., 1971, Cadmium in the environment: U.S. Dept. Commerce Tech. Rept. APTD–0681, 353 p.

Gunn, S. A., Gould, T. C., and Anderson, W.A.D., 1964, Effect of zinc on carcinogenesis by cadmium: Soc. Exp. Biol. Med. Proc., v. 115, p. 653.

——1968, Mechanisms of zinc, cysteine and selenium protection against cadmium induced vascular injury to mouse testis: Jour. Reprod. Fert., v. 15, p. 65..

Hammer, D. I., Finklea, J. F., Creason, J. P., Sandifer, S. H., Keil, J. E., Priester, L. E., and Stara, J. F., 1971, Cadmium exposure and human health effects, *in* Hemphill,

D. D., ed., Trace substances in environmental health—V: Columbia, Univ. Missouri, p. 269.

Harman, D., 1956, Aging: A theory based upon free radical and radiation chemistry: Jour. Gerontology, v. 11, p. 298–300.

Hartz, J. W., and Deutsch, H. F., 1972, Subunit structure of human superoxide dismutase: Jour. Biol. Chem., v. 247, p. 7043–7050.

Heindl, R. A., 1970, Cadmium, *in* Mineral facts and problems: U.S. Dept. Interior, Bur. Mines Bull., no. 650, p. 515–526.

Hsu, J. M., Anthony, W. L., and Buchanan, P. J., 1969, Zinc deficiency and incorporation of 14C-labeled methionine into tissue proteins in rats: Jour. Nutrition, v. 99, p. 425.

Jacobs, E. E., Jacob, M., Sanadi, D. R., and Bradley, L. B., 1956, Uncoupling of oxidative phosphorylation by cadmium ion: Jour. Biol. Chem., v. 223, p. 147.

Jaeger, R. J., and Rubin, R. J., 1972, Migration of a phthalate ester plasticizer from polyvinyl chloride blood bags into stored human blood and its localization in human tissue: New England Jour. Med., v. 287, p. 1114–1118.

Kagi, J.H.R., and Vallee, B. L., 1961, Metallothionine: A cadmium and zinc-containing protein from equine renal cortex: Jour. Biol. Chem., v. 236, p. 2435.

Larson, W. E., Clapp, C. E., and Dowdy, R. H., 1972, Interim report on the agricultural value of sewage sludge: St. Paul, Minn., USDA, ARS and Soil Science Dept., Univ. Minnesota, Metropolitan Sewer Board.

Little, J. B., 1968, Cellular effects of ionizing radiation: New England Jour. Med., v. 278, p. 308-315, 369-376.

McCord, J. M., and Fridovich, I., 1969, Superoxide dismutase. An enzymatic function for erythrocuprein (hemocuprein): Jour. Biol. Chem., v. 244, p. 6049–6055.

——1970, The utility of superoxide dismutase in studying free radical reactions II. The mechanism of the mediation of cytochrome c reduction by a variety of electron carriers: Jour. Biol. Chem., v. 245, p. 1374–1377.

Morgan, J. M., 1969, Tissue cadmium concentrations in man: Arch. Int. Med., v. 123, p. 405.

Moulds, D. E., 1969, Cadmium, *in* Minerals yearbook-I: U.S. Dept. Interior, U.S. Govt. Printing Office, p. 235–240. (See also articles with the same title in the yearbooks for 1945, 1949, 1953, 1957, 1961, and 1965.)

Parisi, A. F., and Vallee, B. L., 1969, Zinc metalloenzymes: Characteristics and significance in biology and medicine: Am. Jour. Clin. Nutr., v. 22, p. 1222.

Perry, H. M., Jr., 1971, Trace elements related to cardiovascular disease, *in* Cannon, H. L., and Hopps, H. C., eds., Geochemical environment in health and disease: Boulder, Colorado, Geol. Soc. America Mem. 123, p. 179.

Perry, H. M., Jr., Tipton, I. H., Schroeder, H. A., Steiner, R. L., and Cook, M. J., 1961, Variation in the concentration of cadmium in human kidney as a function of age and geographic origin: Jour. Chron. Dis., v. 14, p. 259.

Perry, H. M., Jr., Erlanger, M., Yunice, A., and Perry, E. F., 1967, Mechanism of acute hypertensive effect of intra-arterial cadmium and mercury in anesthetized rats: Jour. Lab. Clin. Med., v. 70, p. 963.

Perry, H. M., Jr., Erlanger, M., Yunice, A., Schoepfle, E., and Perry, E. F., 1970, Hypertension and tissue metal levels following intravenous cadmium, mercury and zinc: Am. Jour. Physiol., v. 219, p. 755.

Perry, H. M., Jr., Perry, E. F., and Purifoy, J. E., 1971, Antinaturitic effect of intra-muscular cadmium in rats, *in* Friberg, L., Piscator, M., and Nordberg, G., Cadmium in the environment: U.S. Dept. Commerce Tech. Rept. APTD–0681.

Pinkerton, C., Creason, J. P., Shay, C. M., Hammer, D. I., Buechley, R. W., Murthy,

G. K., 1971, Cadmium content of milk and cardiovascular disease mortality, *in* Hemphill, D. D., ed., Trace substances in environmental health—V: Columbia, Missouri, Univ. Missouri, p. 285.

Pulido, P., Fuwa, K., and Vallee, B. L., 1966a, A determination of cadmium in biological materials by atomic absorption spectroscopy: Ann. Biochem., v. 14, p. 393.

Pulido, P., Kagi, J.H.R., and Vallee, B. L., 1966b, Isolation and some properties of human metallothionine: Biochem., v. 5, p. 1768.

Sandstead, H. H., 1973, Zinc nutrition in the USA: Am. Jour. Clin. Nutr., v. 26, p. 1251.

Sandstead, H. H., Prasad, A. S., Schulert, A. R., Frarid, Z., Miale, A., Jr., Bassilly, S., and Darby, W. J., 1967, Human zinc deficiency endocrine manifestation and response to treatment: Am. Jour. Clin. Nutr., v. 20, p. 422.

Sandstead, H. H., Lanier, V. C., Shepard, G. H., and Gillespie, D. D., 1970, Zinc and wound healing: Am. Jour. Clin. Nutr., v. 23, p. 514.

Sandstead, H. H., Gillespie, D. D., and Brady, R. N., 1972, Zinc deficiency: Effect on brain of the suckling rat: Pediat. Research, v. 6, p. 119.

Schroeder, H. A., 1965, Cadmium as a factor in hypertension: Jour. Chron. Dis., v. 18, p. 647.

Schroeder, H. A., and Balassa, J. J., 1961, Abnormal trace metals in man: Cadmium: Jour. Chron. Dis., v. 14, p. 236.

Schroeder, H. A., Nason, A. P., Tipton, I. H., and Balassa, J. J., 1967, Essential trace metals in man: zinc. Relation to environmental cadmium: Jour. Chron. Dis., v. 20, p. 179–210.

Schroeder, H. A., Nason, A. P., and Mitchner, M., 1968, Action of a chelate of zinc on trace metals and hypertensive rats: Am. Jour. Physiol., v. 214, p. 796.

Simon, F. P., Potts, A. M., and Gerard, R. W., 1947, Action of cadmium and thiols on tissues and enzymes: Arch. Biochem., v. 12, p. 283.

Terhune, M. W., and Sandstead, H. H., 1972, Decreased RNA polymerase activity in mammalian zinc deficiency: Science, v. 177, p. 68.

Ulmer, D. D., and Vallee, B. L., 1969, Effects of lead on biochemical systems, *in* Hemphill, D. D., ed., Trace substances in environmental health—II: Columbia, Univ. Missouri, p. 7.

USDA and TVA, 1964, Superphosphate: Its history, chemistry and manufacture.

Voors, A. W., Shuman, M. S., and Gallagher, P. N., 1975, Atherosclerosis and hypertension in relation to some trace elements in tissues: World Rev. Nutrition and Dietetics, v. 20, p. 299.

Winston, R. M., 1971, Cadmium fume poisoning: British Med. Jour., v. 2 (5758), p. 401.

Wood, S., 1968, Vinyl bottles, what now?: Modern Plastics, v. 45 (12), p. 78–82.

Zavon, M. R., and Meadows, C. D., 1970, Vascular sequelae to cadmium fume exposure: Am. Ind. Hyg. Assoc. Jour., v. 31, p. 180–182.

PAPER PRESENTED AT THE 1972 ANNUAL MEETING OF THE GEOLOGICAL SOCIETY OF AMERICA IN MINNEAPOLIS, MINNESOTA

MANUSCRIPT RECEIVED BY THE SOCIETY SEPTEMBER 17, 1973

REVISED MANUSCRIPT RECEIVED SEPTEMBER 29, 1974